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Post-Approval Research: Safety Net or Power Tool?

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Uncover new markets?

Reinforce consumer confidence? Those are just some of the power uses for phase IV testing.

The method of releasing a new product into the marketplace is a delicate balancing act. A developer naturally wants to release its product ASAP. However, the developer also knows the product has to undergo serious testing before it can safely be made publicly available.

Post-approval research is the responsible solution to this dilemma. Also known as phase IV testing, this method allows a product to prove its real-world worth through patient health improvement while simultaneously demonstrating its long-term safety. This method enables knowledgeable practitioners to prescribe the product in confidence, which makes the product more valuable. It also sets up mechanisms to:

- Evaluate product utilization patterns
- Explore market and label expansion opportunities
- Provide a steady pipeline of data for scientific publications and presentations

A GOOD TARGET

Let's say your company has a new product under development. First you find the molecule or made a device, then figured out how to deliver it in a way that improves diagnostics, effects a cure, delays disease progression or improves quality of life. Congratulations, your product has demonstrated its efficacy through studies conducted under ideal circumstances.

The next challenge is to demonstrate "effectiveness" or the extent

to which medical interventions can achieve health improvements in real practice settings. After finishing early phase studies, you should be laying the groundwork for post-approval clinical research. Such programs are opportunities to cultivate customers, build market share, demonstrate value to key customer segments and track product adoption. They also provide a chance to demonstrate your company's commitment to fighting a particular disease, to set the foundation for meeting regulatory needs and commitments, or any legal challenges that may arise.

POST-APPROVAL ASPECTS

Drive appropriate and rapid adoption, and set the stage for persistency through strong relations with practitioners.

In pre-approval studies, you work with influential specialists and key opinion leaders; you pay the necessary fees for these roles; and you work with specialized CROs to conduct registry-quality trials of efficacy and safety. For post-approval work, you need different investigators, and partners who specialize in the post-launch arena.

Investigators in post-approval studies are representative of those who typically treat patients. Since the site payments are modest, post-approval studies—especially registries—need to offer value-added services to induce participation. Successful programs offer regular Web-based seminars and create value for physicians through benchmarking data and on-line

treatment guidelines. Post-approval programs generate a steady pipeline of clinically relevant publications and scientific presentations, thus arming the field-based sales force and medical science liaisons with lots of relevant collateral.

Keep your eye on the marketplace to discover clues that may help broaden your label, understand current practices and gain competitive intelligence, and monitor safety in conditions of long-term product use.

You need to monitor how your product is being used, where it fits in the therapeutic regimen, the resources needed to deliver appropriate care, and what makes your intervention useful and relevant to providers and patients. This is an opportunity to identify successful, practical strategies in the long-term management of diseases, and to monitor the impact of a variety of treatment modalities. You can also gain valuable insight about off-label uses that you may wish to explore more formally in pursuit of new indications.

Some post-approval research programs are conducted as a condition of regulatory approval, as formal post-marketing commitments. These programs can also be undertaken as a means to proactively respond to any perceptions of safety issues, such as weak signals that were detected during Phase II and III trials. Rather than publicize these programs as safety programs, they can be embedded in a broader, multipurpose program so as not to focus external attention solely on risk.

In research on an entire disease area, not just a product or a procedure, you conduct active surveillance of users and relevant comparison groups. If a safety signal is detected, you have the information at hand to evaluate whether these events are characteristic of people being treated for the condition of interest or if the signals are most likely to be a result of using the product. You should consider this as an investment in a resource that will help protect the product and company through the ability to quickly evaluate the regulatory and legal challenges using real-world evidence. For

example, reports suggested a higher incidence of cardiovascular events among users of a new product to treat hair loss, but research showed that bald men are at higher risk of these events, regardless of product use. Clinically relevant data makes for a strong defense.

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Develop effective pricing and reimbursement strategies

Companies need to approach pricing and reimbursement with an eye toward country-specific needs and key customer segments—including governments, private health insurers (national and regional health plans), academic and teaching institutions, long-term care facilities and employers. Showing a direct cost savings is the most persuasive approach.

Improvements in quality of life are becoming increasingly important, especially if they can be linked to reduced healthcare costs. While you need to show value to all customers, the metrics will vary according to customer. In the United States, large employers dictate the terms of contracts with insurers. If a treatment or procedure results in greater productivity or fewer days lost from work, an employer would be more likely to insist on coverage for that intervention.

Strategies for optimal pricing and reimbursement are changing

rapidly as competition increases within therapeutic areas and buyers demand more substantiation of product value. A dramatic shift in the visibility of economic considerations was evident in 1999 when the UK National Health Service created the National Institute for Clinical Excellence (NICE). NICE's mission was, in part, to produce clear guidance in an effort to improve quality of health care by finding products that are "practical and affordable." NICE reviews information about a product's clinical and cost effectiveness when there was confusion or uncertainty about the value of a drug or a device. Once NICE guidance is published, health professionals must take the Institute's guidance fully into account when exercising their clinical judgment.

In 2000, the Academy of Managed Care Pharmacy (AMCP) in the United States issued guidelines for standardized formulary submissions from pharmaceutical companies. A standard dossier requires information on economic value relative to alternative therapies, safety and effectiveness, and seeks information on unpublished studies, data on off-label indications, and related disease management strategies. Pharmacy committees use the data to evaluate whether a drug will be included in an insurer's formulary—whether it will receive any reimbursement, and if so, how much.

In the United States, most managed care organizations have adopted tiered co-payments for drugs where generics received the lowest co-payments from consumers and newer, branded drugs, the highest. These benefit programs have become a powerful means for changing consumer behavior and driving sales.

Consider the results of a study of the effects of a tiered pharmacy benefit, comparing co-payment differences for branded products of \$15-\$18, using data from four commercial health insurance plans from one state during 1998 and 1999. The comparison group had no tiered brand co-payments. The study looked at statins, ACE inhibitors and proton pump inhibitors.

For all three drugs, tiered prescription co-payments were consistently associated with a significant shift from

A win in a head-to-head trial can provide a tremendous boost to sales.

non-preferred to preferred brand medications. Tier effect increased with age of beneficiary, and the effect was greater with repeated use of medication.

In some situations, you may need to take on some risk to get your product onto a formulary or accepted for reimbursement. A good, focused clinical research program can provide you with access to real-time data that will quantify the return on investment for risk-sharing programs. Tools like Web-based data collection programs are especially useful here, because they can be tailored to your needs, run on a large scale (at relatively low cost), and offer immediate access to data.

POST-MARKETING STUDY TOOLS

Can't I just mine data from my pre-approval studies?

Do you think about spending more on clinical research now that your product is almost ready for launch? Considering the pressures on resources and finances, you may wonder if you could mine the data you already collected to meet your post-approval needs.

But think about your pre-approval clinical trials and their intended purposes. You needed to prove efficacy and safety. You chose the cleanest, most narrowly defined study groups possible—they had the condition of interest, and as few other illnesses as possible. Through deliberate design of your protocols, you required attentive use of your product and regular

doctor visits with sophisticated testing to monitor compliance and progress. And how did you know that your product was effective? You compared your treatment to a placebo—and your product worked better than nothing!

With good reason, data from randomized controlled clinical trials are regarded as the gold standard of scientific evidence for getting new drugs and devices approved for commercial marketing. But the relevance of these data to real-world use is quite limited.

The shift in focus from optimal use in narrowly defined populations to broad use in a wide variety of patients requires different tools. Rather than control every aspect of clinical research, this is the time to control very little, and then observe what happens.

The average medical practitioner faces large numbers of patients, practice management guidelines that may restrict access to specialists or make close follow-up challenging, and the need to find defensible billing codes to get the highest reimbursement for time spent during the visit. What are the best treatments for someone with these risk factors and co-morbidities? Which treatments are covered? What can the patient afford?

The best post-approval research addresses (or helps to generate) substantive hypotheses about outcomes and health economics, and is designed to monitor serious risks in widespread and long-term continuous

use. The most common tools at this stage are field trials and observational studies. The randomized clinical trial (RCT) still has a place in post-approval research, though study populations are more heterogeneous and data collection is more focused, with shorter case report forms.

Randomized clinical trials

Post-approval RCTs are designed to test clinical effectiveness and/or safety hypotheses about the anticipated typical use of the drug in routine clinical practice. These are often referred to as large streamlined trials (LSTs). Patients can be randomized to treatment arms that compare standard care to enhanced care, and the endpoints that are evaluated include medication adherence, patient satisfaction, and use of specific health care services. LSTs are also useful in safety studies—however, in these situations, companies should pay particular scrutiny to the ethics of deliberately exposing patients to a treatment or procedure that may be harmful. Some safety trials actually involve recruiting known product users and withholding treatment (or substituting an alternative treatment) in one arm of the study.

There is a move to promote pragmatic or practical clinical trials (PCTs), which are designed specifically to answer questions posed by policy makers. PCTs compare clinically relevant treatments (no placebos) and study a broad range of outcomes. Although the concept is attractive, there are few funders of such research.

Sometimes companies sponsor head-to-head trials, another form of PCT. Those are risky ventures,



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Sophisticated testing is the best way to monitor compliance and progress.



Registries help identify high-risk groups, such as children or the elderly.

especially since all clinical trials now need to be registered at their outset, in a public forum (see www.clinicaltrials.gov.) A win in a head-to-head trial can provide a tremendous boost to sales. GlaxoSmithKline compared its drug for heart failure, carvedilol, to Novartis' metoprolol tartrate at COMET (carvedilol or metoprolol European Trial); the study showed that carvedilol had fewer deaths than the comparator. Yet, there are many other examples that revealed that the competitor's product was equivalent and more economical, clinically superior, or safer.

Registries and Non-Experimental Research

Post-approval observational studies are a logical and attractive choice for controlled clinical trials. In contrast, longitudinal studies have limited inclusion and exclusion criteria, and generally accept "all comers" for study. Though observational studies lack randomization, they usually have large numbers of subjects, which allows them to address differences between subgroups through analytic procedures like stratification, rather than by exclusion through design. Longitudinal studies, also referred to as "registries," are basically platforms for observational follow-up studies to track groups of interest, evaluate health resource utilization patterns, develop clinical

effectiveness and safety hypotheses, detect rare adverse drug reactions, and/or improve market awareness of products.

Registries focus either on specific products and procedures, or more general conditions, enrolling patients with a specific drug, device or diagnosis (as with disease or pregnancy) and following them over time. Registries can be thought of as trials with only one arm.

Since registries are observational, not experimental, they do not dictate how interventions are used or how conditions are treated; thus, they provide unique opportunities to study off-label use. Similarly, they are ideal vehicles for obtaining information on potentially high risks groups, like pregnant women, the elderly and young children.

Although no human subject review board would permit deliberate exposure of these groups to potentially harmful agents in an experimental setting, we expect to see much broader use once a product is marketed, no matter how specific the package insert.

KEY DESIGN CONSIDERATIONS Comparators

It is essential to use meaningful comparators for economic research as well as for safety research. Health economics evaluations compare new products or treatments to their major competitors, or to whatever practice

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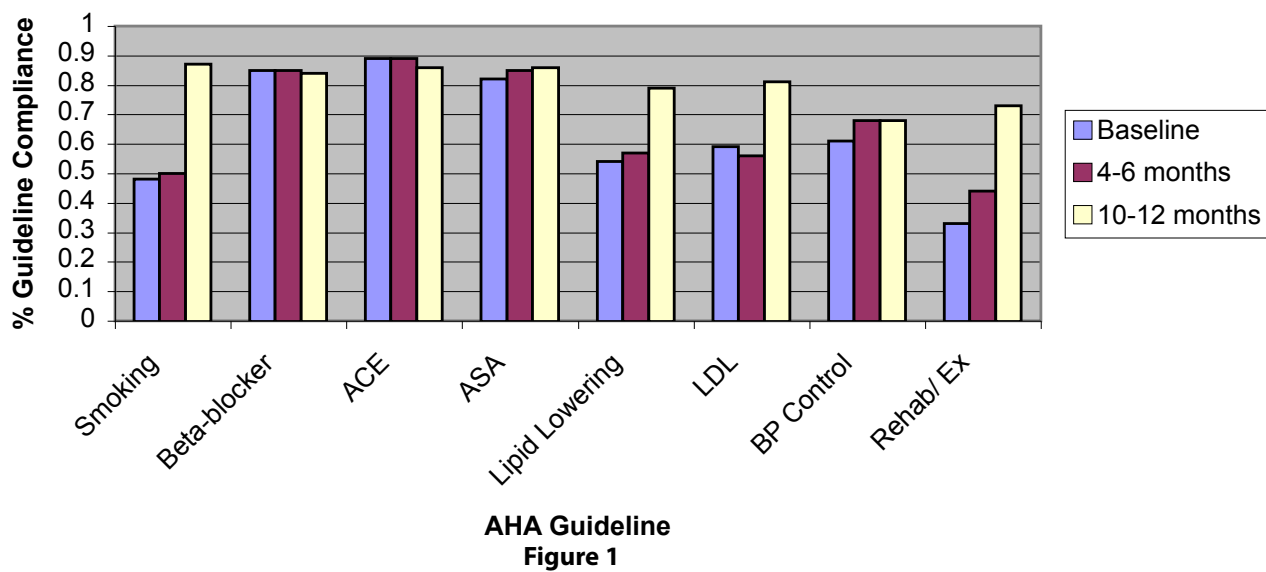
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12 Month GWTG Pilot Results



is considered the gold standard by the majority of practitioners. For safety research, data on contemporaneous comparators—information collected on similar patients through similar methods at about the same point in calendar time—allow for epidemiologic investigation of effects according to various combinations of risk factors, while controlling for factors that change over time, such as improved medical practices.

Just my product?

The question of benchmarks or comparators also comes into play when deciding whether to collect data about other treatments for the condition of interest, including information about your competitor's products. For condition-based registries, there are no predefined interventions. You run the risk here of being swamped with information about competing products or "watchful waiting" disease management. To address these potential imbalances and secure enough information on your product, you may limit the number of comparator patients enrolled in the registry (or observational study) if the cost-per-patient is high.

Length of follow-up

Your company may need to extend follow-up in post-approval research.

The one to two months of observation commonly used in studies of efficacy may not be persuasive enough when cast in the context of broader health costs. Longer follow-up is also useful for safety studies and post-marketing commitments. Some health risks may not be evident soon after product initiation. The cardiovascular effects that caused Merck to remove Vioxx from the market only became evident after about 18 months of continuous product use.

Observe or influence

Post-approval studies can be designed to stimulate preferred behavior rather than merely to observe. Registries can be set up as quality improvement (QI) programs that include easily accessible treatment guidelines and reinforce these messages through structured communication programs. Consider the "Get With the Guidelines" program for secondary prevention of cardiovascular disease, a QI program from the American Heart Association that won an "Innovation in Prevention Award" from the US Secretary of Health and Human Services. The program used Web-based management tools to collect data and provide on-line feedback, and employed a system of didactic and best-practice presentations to participants. The results showed clinically and statistically significant improve-

ments in the use of lipid treatments, cardiac rehabilitation referral and smoking cessation counseling, among others. Even more impressive, these improvements persisted over time (see figure 1). QI programs can be used to observe behavior when best practices are introduced and re-enforced, and can actually help drive appropriate sales for therapeutic categories.

INVESTING IN SUCCESS

Balanced post-marketing clinical research is a sign of good product stewardship—and also makes for good business. Valuable information is gained that will guide appropriate product use, which is also valuable for promotion and as a tool to accelerate sales. When powering up a marketing and clinical outreach program, you are also implementing a product and company safeguard that will monitor safety in real-world settings. Thinking through all post-marketing needs well before product launch will allow you to conduct cost-efficient, multipurpose post-approval research that will ultimately improve product and patient outcomes. ~

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